

# Breast cancer screening policy—good science should trump bad politics

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Dr. Steven Narod's comments on breast cancer screening (Countercurrents: Is now the right time to pull the plug on mammography?) are troubling in that they suggest a lack of familiarity with or understanding of the science, and possibly a political anti-preventive-medicine bias. It is hard to know where to begin the critique, but one could start with his suggestion that the "mere" 15% reduction in breast cancer mortality attributed to mammography screening by The Canadian Task Force on Preventive Health Care (CTFPHC) is "derisory." In our society, such a reduction would be considered valuable and noteworthy. For example, a 15% decrease in the U.S. infant mortality rate, observed by the U.S. Centers for Disease Control and Prevention, was highly publicized<sup>1</sup>. In Canada, a 15% decrease in breast cancer deaths means that 800 fewer women would die of breast cancer each year.

But the potential lifesaving from breast cancer screening is considerably greater than the 15% acknowledged by the CTFPHC. Narod stated that the CTFPHC performed a "meta-analysis of the literature" on breast cancer screening. Actually it did not. The data analysis was performed by a separately contracted group who carried out a review of reviews, two of which were systematic reviews previously done by the CTFPHC and the U.S. Preventive Services Task Force<sup>2,3</sup>. Essentially, it was a re-mastication of trial data that had already been analyzed and meta-analyzed multiple times<sup>4-7</sup>, and the value of repeated systematic reviews of the same data has been called into question<sup>8</sup>. The CTFPHC review included only randomized controlled trials that had been conducted from 25 to almost 60 years earlier, when screening and treatment were both relatively primitive compared with today's methods. Valuable data from modern observational studies were ignored. Furthermore, the external analyses did not undergo formal journal peer review, but were published on the CTFPHC Web site.

A full meta-analysis of data from more than 40 breast cancer screening trials of varying design was conducted by an International Agency for Research on Cancer Working Group in 2014<sup>5</sup>. That analysis, which was ignored by the CTFPHC review, was performed by experts from 16 countries, including epidemiologists who were experienced in the analysis of screening-trial data, assisted by content experts in medical imaging who were nonvoting members of the Working Group. Its conclusion was that being invited to be screened resulted in a 23% reduction in the risk of death from breast cancer; women who attended mammographic screening had a higher reduction in risk, estimated at about

40%. That result is consistent with results from multiple modern observational studies of outcomes from service screening programs in several countries, which showed reductions in the number of breast cancer deaths of between 30% and 44% for women beginning screening from age 40<sup>9,10</sup>. That mortality benefit comes in addition to the reductions in morbidity that accrue when disease is treated at an earlier stage or when the lesion is smaller (or both)<sup>11-15</sup>.

Narod, referring to his own previously published opinion, also suggests that the difference in breast cancer deaths between participants and nonparticipants in the large Pan-Canadian Study of Mammography Screening and Mortality from Breast Cancer<sup>9</sup> resulted from a prevalent population of women in the nonparticipating group who already had breast cancer at the onset of the observation period. But the study design is one of incidence-based mortality, in which the date of the detected first breast cancer is taken from provincial cancer registries and, therefore, would be within the defined observation period. That approach effectively eliminates breast cancers diagnosed before the observation period, except for the few women who moved between provinces after diagnosis of their breast cancer (accounting for only a small number of possible breast cancer deaths)<sup>a</sup>.

Narod, with colourful language ("bruited," "meretricious," "nugatory," "calumnists") attempts to use the failure of the Canadian National Breast Screening studies (CNBSS) to demonstrate mortality reduction to justify his argument that there is essentially no mortality benefit from breast cancer screening with mammography. The CNBSS trials have been discredited by many experts for multiple reasons—insufficient size to attain power to demonstrate a plausible mortality reduction, and suspicions of flawed randomization and poor quality of the mammograms<sup>16-19</sup>. The cancers detected in the mammography arms of the trial were, on average, only 2 mm smaller in diameter than those in the control arms. Narod has stated that mis-randomization in the CNBSS was "impossible"; however, as far back as 1993, an eminent epidemiologist explained exactly how the randomization in the trials could have been subverted by a well-meaning staff person because of weak design in the registration process: the participant was entered into an open-book registration log *after* clinical examination of the breast (the control intervention) had already taken place<sup>16,17</sup>. Boyd *et al.*<sup>16</sup> estimated that the probability of the observed

<sup>a</sup> Coldman A. Personal communication. 5 February 2019.

large imbalance of poor-prognosis cancers in the prevalence round of screening in the CNBSS (with more of those cancers being in the mammography arm of the trial) occurring because of random chance was less than 3 per 1000!

Why is Narod surprised at the suggestion that modern mammography “in the real world” probably has greater sensitivity and specificity for smaller cancers than was the case in 1977 when imaging in the Swedish trials<sup>20</sup> took place? There is ample evidence for such improvement<sup>21,22</sup>.

Narod goes on to state that “Part of the mission of the Task Force is to consider all the prevalent opinions and to separate those of disinterested parties from those of parties with something to gain. The fact that they are not practitioners of the art of mammography is what makes them credible.” A few errors here. First, it is not really the *opinions* of individuals that are of prime importance, but the *evidence* that comes from carefully conducted studies. Not being a practitioner of mammography might remove one type of conflict of interest, but does not in itself confer competence or credibility in evaluating the evidence. In the case of the CTFPHC and its guidelines, it can be argued that some basic errors in the data interpretation arose precisely because of ignorance of the details of mammography screening.

Narod’s comments, rather than supporting “pulling the plug” on mammography screening, actually highlight the inadequacy and incompleteness of the CTFPHC review of the evidence concerning screening and its failure to compare benefits and harms quantitatively on a common scale. The potential mortality reduction is more likely to be 35% than 15%. Where Narod and I agree is that, if screening is effective (which it is), the CTFPHC has not made a solid case that overdiagnosis (overdiagnosis) and “false positive” screens (“harms”) come anywhere near the expected benefits that come from screening.

Narod’s speculations regarding the origins of breast cancer metastasis are interesting, if not original. They lack validation and represent only one of several possible explanations of his observation of a nonlinear relationship between tumour size at diagnosis and the presence of distant metastasis. Most importantly, they appear to be inconsistent with the meta-analyses of the randomized controlled trials, that, even with the inclusion of the flawed CNBSS results, demonstrate that screening is effective in reducing breast cancer mortality.

Narod’s suggestion of “pulling the plug” on mammography screening, an intervention that is currently helping to save lives, is poorly considered, irresponsible, and dangerous. *Primum non nocere*.

#### CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology*’s policy on disclosing conflicts of interest, and I declare the following interests: I participate in a research collaboration with GE Healthcare on topics in breast tomosynthesis and contrast-enhanced mammography, in which funds to cover some research costs are provided to my institution. I also hold shares in Volpara Health Technologies, a company that produces software for breast imaging.

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